Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-17 are pending in the application, with claim 1 being the independent claim. The Examiner withdrew claims 6, 7 and 10-13 from consideration.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 103

The Examiner has rejected claims 1-5, 8, 9 and 14-17 under 35 U.S.C. §103(a) as allegedly being obvious over Gowri *et al.* (AJH 1992; 12:744-766) and Gowri *et al.* (Am. J. Physiol. Endocrinol. Metab., 2000; 279:E593-E600) in view of Copp *et al.* (U.S. Pat. No. 4,572,913). (*See* Office Action at page 2). Applicants respectfully traverse the rejection.

The Examiner asserts that Gowri *et al.* (AJH) (hereinafter "Gowri 1999") teach the "use of masoprocol, a lipoxygenase inhibitor for the lowering of blood pressure." (Office Action at page 2). The Examiner further asserts that Gowri *et al.* (Am. J. Physiol. Endocrinol. Metab.) (hereinafter "Gowri 2000") teach that "masoprocol, a li[p]oxygenase inhibitor lowers serum triglycerides in rats." (Office Action at page 2). The Examiner concedes that the references differ from the claimed invention in the "use of the claimed li[p]oxygenase inhibitor, a phenyl pyrazoline derivative." (Office Action at page 2). However, the Examiner cites Copp *et al.* (hereinafter "Copp") to teach "the use of phenyl pyrazoline derivatives as lipoxygenase inhibitors." (Office Action at page 2). The Examiner concludes that it would have been

> obvious to a person skilled in the art to use a phenyl pyrazoline for the treatment of hypertension and elevated blood triglycerides, motivated by the teachings of Copp et al., reference, which teaches phenyl pyrazole derivatives as lipoxygenase inhibitors.

(Office Action at page 2).

With respect to the motivation to combine the art, the Examiner alleges that:

> [o]ne skilled in the art would have been motivated to combine the teachings of the above references, since Gowri et al. teach the use [of] a li[p]oxygenase inhibitor for treatment of hypertension and lowering serum triglyceride, and the other relates to the use of phenyl pyrazole derivatives as lipoxygenase inhibitor[s]. The substitution of one lipoxygenase inhibitor for another would have been obvious to a person skilled in the art in the absence of evidence to the contrary.

(Office Action at pages 2-3). Applicants respectfully disagree with the Examiner's conclusions.

The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The USPTO has recently published guidelines for Examiners in determining whether claims are non-obvious under the *KSR* holding. *See* Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International v. Teleflex Inc.* Fed. Reg. Vol. 72, pp. 57526 to 57535 (October 10, 2007), (hereinafter "Examination Guidelines"). According to the Examination Guidelines, a rejection that is based on a substitution of one element for another must include an

explanation that the substitution would lead to a predicable result. Specifically, the Examiner must establish:

> (1) a finding that the prior art contained a method which differed from the claimed method by the substitution of some element with other elements;
> (2) a finding that substituted elements and their functions were known in the art;
> (3) a finding that one of ordinary skill in the art would have substituted one known element for another, and the results of the substitution would have been predictable;
> (4) any additional findings based on the *Graham* factual findings.

See id.

Additionally, a *prima facie* case of obviousness cannot be established unless all of the claim elements are taught or suggested by the cited references. *See In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42 (Fed. Cir. 2002); *In re Rijckaert*, 9 F.3d 1531, 1533 (Fed. Cir. 1993). The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). The Examination Guidelines allow for factors other than the disclosure of the cited references to establish a basis for finding obviousness. *See id.* at 57528 ("Prior art is not limited just to the references being applied, but includes the understanding of one ordinary skill in the art."). However, the Examination Guidelines also require that the Examiner articulate with particularity the reasons to support the conclusion that the elements are well-known and that the combination is predictable. *See id.*

1. The Examiner did not articulate with particularity the reasons to support the finding that one skilled in the art would have substituted one element for another.

The United States Supreme Court in *KSR* has further clarified the requirements for obviousness analysis under 35 U.S.C. § 103(a) by noting that the analysis supporting a rejection should be made *explicit*, and that it was "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. The Court specifically stated:

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was *an apparent reason* to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, *this analysis should be made explicit.* (*KSR*, slip opinion, page 14, *citing In Re Kahn*, 441 F. 3d 977,988 (CA, Fed. 2006) ([R]ejections on obviousness grounds *cannot be sustained by mere conclusory* statements, instead, there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness").

KSR at 1740-41 (emphasis added).

The Applicants assert that the Examiner has merely made conclusory statements and has failed to provide any articulated or explicit reasoning for combining the references to support an obviousness rejection. The Examiner appears to have made the improper determination that masoprocol's status as a lipoxygenase inhibitor suggests that it would *only* act as a lipoxygenase inhibitor and, furthermore, that any effects masoprocol may have on rats would also hold true for other lipoxygenase inhibitors. As

will be discussed in this Reply, the Gowri references disclose that masoprocol has effects *outside* of the lipoxygenase pathway, and its use in lowering blood pressure and serum triglycerides in rats is not proven by the cited references to be elicited through the lipoxygenase pathway. The Examiner's reasoning to combine the "known" elements is that the "substitution of one lipoxygenase inhibitor for another would have been obvious to a person skilled in the art in the absence of evidence to the contrary." Rejections on obviousness grounds cannot be sustained by such mere conclusory statements; therefore, Applicants respectfully request this rejection be withdrawn.

2. A person of ordinary skill in the art would not have found the claimed invention predictable.

While the Office sets forth a number of rationales by which a determination of obviousness may be made (Examination Guidelines at 57529), a common thread throughout requires that the prior art, in combination with the knowledge ascribed to the person of ordinary skill in the art, provide sufficient information to make the claimed invention fully and easily predictable. Applicants assert that a person of ordinary skill in the art would *not* have found the claimed invention predictable. Gowri 1999 does *not* establish masoprocol's lipoxygenase mechanism of action. Instead, Gowri 1999 *speculates* that the observed effects were because of masoprocol's lipoxygenase inhibitory activity. The authors declare "the mechanistic explanation for the hemodynamic and metabolic effects of masoprocol documented in this study are not self-evident." Gowri 1999, p.746. Given the nature of the discussion by the authors, there is no indication of what compounds would work, or if the lipoxygenase pathway is even responsible for the observed effects. For example, the authors provide a possible

mechanistic explanation by speculating that "masoprocol increases insulin sensitivity in fructose-fed rats, thereby leading to a concomitant decrease in blood pressure and plasma insulin and triglyceride concentrations." Gowri 1999, p.746. The authors also propose that masoprocol could be eliciting an effect on magnesium metabolism or acting as an antioxidant. *See* Gowri 1999, p.746. Even if the effects observed by masoprocol in the Gowri references were attributable to inhibition of the lipoxygenase pathway, the references show no evidence that it is *5-lipoxygenase* inhibition. As disclosed in the Applicants' specification at paragraph [0008], other types of lipoxygenase inhibition can occur (e.g. 12-lipoxygenase inhibition). Such a possibility only furthers the unpredictability of the claimed invention.

As further confirmed and explained in Gowri 2000, "[a]lthough a well known lipoxygenase inhibitor, the profound metabolic effects of masoprocol only recently became apparent (8, 14, 26). The possibility that these effects may not be mediated by the lipoxygenase pathway must be considered, given the observation that esculetin, another lipoxygenase inhibitor, had no anti-lipolytic activity." Gowri 2000, p. E599. Given that the authors specifically pointed out that the effects may not be mediated by the lipoxygenase pathway in both Gowri 1999 and Gowri 2000 is further evidence that it was not understood at the time of this invention if other lipoxygenase inhibitors would work or how they would work (i.e. whether the lipoxygenase pathway is even implicated).

Neither Gowri reference shows that lipoxygenase inhibitors, acting through the 5-lipoxygenase pathway, act to lower serum triglycerides or hypertension. The speculative

nature of both Gowri references in linking the lipoxygenase pathway to masoprocol's observed effects and the observation of another (non-phenyl pyrazoline derivative) lipoxygenase inhibitor (esculetin) not having the same antilipolytic properties that masoprocol has would certainly not rise to the level of providing predictability and motivating one skilled in the art to substitute one lipoxygenase inhibitor for another. As alleged by the Examiner, "[t]he substitution of one lipoxygenase inhibitor for another would have been obvious to a person skilled in the art *in the absence of evidence to the contrary*." Office Action, p. 3 (emphasis added). The Applicants assert that Gowri 2000 provides such evidence to the contrary since esculetin, a lipoxygenase inhibitor, cannot be substituted for masoprocol, another lipoxygenase inhibitor, to lower lipolytic activity in rats.

3. There is no reasonable expectation of success in combining the Gowri references with Copp to arrive at the claimed invention.

A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *See* M.P.E.P. § 2141.02(VI) (citing *W.L. Gore & Associates, Inc.* v. *Garlock*, Inc., 721 F.2d 1540 (Fed. Cir. 1983)); *see also Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1093-94 (Fed. Cir. 1985) ("The well established rule of law is that each prior art reference must be evaluated as an entirety...."). That is, "[t]here is no suggestion to combine...if a reference teaches away from its combination with another source." *Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999); *see also KSR* at 12 (reaffirming "the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be

nonobvious") (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). A reference teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, *or would be led in a direction divergent from the path that was taken by the applicant*...." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (emphasis added).

Applicants submit that there is no reasonable expectation of success in combining the two Gowri references with Copp, to arrive at the instantly claimed invention of administering a 5-lipoxygenase inhibitor to a human subject to treat elevated serum triglycerides or hypertension. Read in their entirety, the two Gowri references actually discourage from substituting any lipoxygenase inhibitor since the references had mixed success with the lipoxygenase inhibitors tested. Gowri 2000 showed that esculetin, another lipoxygenase inhibitor, had no antilipolytic activity in rats. Gowri 1999 only showed an effect on rat blood pressure after treatment with masoprocol. Gowri 1999 did not test any other lipoxygenase inhibitors. At most, Gowri 1999 was an invitation for further research, and Gowri 2000 subsequently complicated the implications of the role of lipoxygenase inhibitors in lipolytic activity by providing mixed results with the lipoxygenase inhibitors tested.

Copp does not rectify the shortcomings of Gowri 1999 and Gowri 2000. The mere disclosure of a single lipoxygenase inhibitor lowering blood pressure and lipolytic activity in rats, followed by disclosure that another lipoxygenase inhibitor does not have the expected effect in lowering lipolytic activity, provides no indication that it would necessarily be successful to use a phenyl pyrazoline derivative (or any other

lipoxygenase inhibitor, for that matter) in the treatment of hypertension or elevated serum triglycerides in a human subject.

For at least the reasons set out above, the scope and content of the art would not have allowed a person of ordinary skill in the art to *predictably* arrive at the claimed invention, as required under *KSR* and the USPTO Examination Guidelines. Therefore, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness and respectfully request that this rejection be reconsidered and withdrawn.

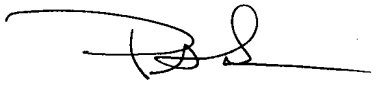
Conclusion

All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider all currently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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